Gastroenteritis in a Taipei emergency department: aetiology and risk factors

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Abstract

A matched case-control study was used to determine pathogens and risk factors associated with gastroenteritis in a Taipei Emergency Department. Viruses (40.0%) were the leading cause of gastroenteritis, with noroviruses the most prevalent (33.2%). Bacteria were found in 26.0% of all cases, mostly suspected diarrheagenic *E. coli* (22.2%), followed by *Salmonella spp.* (5.4%) and *Vibrio parahaemolyticus* (4.2%). *Giardia lamblia* was identified in 16.4% of all cases. Statistical significance was noted for seven risk factors: taking antacids before gastroenteritis (OR = 3.91; 95% CI, 2.13, 7.15), other household members with gastroenteritis (OR = 5.18; 95% CI, 2.09, 12.85), attending a banquet (OR = 1.93; 95% CI, 1.25, 2.98), eating out (OR = 2.35; 95% CI, 1.30, 4.23), drinking bottled water (OR = 1.72; 95% CI, 1.07, 2.75), eating honey peaches (OR = 3.26; 95% CI, 1.24, 8.58), and eating raw oysters (OR = 3.24; 95% CI, 1.02, 10.28). Eating out was identified as the highest risk behavior, as measured by population attributable risk fraction (PAR) (50.9%). Respective PAR values for drinking bottled water, attending a banquet and taking antacids before illness were 19.7%, 19.6% and 17.6%. Of these, additional research on bottled water appears to be the highest priority, because this is the first time it has been identified as a risk factor for gastroenteritis.

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Introduction

There are many studies of risk factors for all-cause and pathogen-specific gastroenteritis among adult cases presenting to primary and secondary hospital settings, but only a limited number of studies was performed in the emergency department (ED) setting. However, the spectrum of pathogens in the community and among cases presenting to hospital services are likely to be very different [1]. One study reported that 37% cultures were positive and *Shigella* was the most commonly isolated pathogen in the ED [2]. Another study did describe a link between eating out (defined as eating anywhere away from one's home) and food poisoning cases at hospital emergency departments, but it did not specify which food was likely to be associated with gastroenteritis [3]. The aims of the present study were to investigate the pathogens and risk factors of acute gastroenteritis cases presenting to the ED.

Materials and Methods

Study design

The study site was the Ren-Ai branch of Taipei City Hospital. The data of 419 patients were collected by the triage nurse from 1 August 2005 to 31 July 2007. The study was approved by the Taipei City Hospital Institutional Review Board. Primary case definitions were (i) at least three loose stools or three instances of vomiting, or (ii) either diarrhoea and/or vomiting plus two or more additional symptoms, including abdominal pain, fever, nausea, blood in the stool, or stool mucus. Patients were excluded from the study if they: were <15 years old; exhibited coughing, a sore throat, or runny nose; or were bedridden (defined as anyone staying in

bed who needs help to get out of bed). Patients were matched 1-to-1 with a non-gastroenteritis control case of the same gender, age (±5 years) and date of ED visit (within 1 month). An additional exclusion criterion was used for the control group: patients aged >65 years old. Follow-up telephone interviews with 329 participants were conducted 7–10 days after the ED visit. Blood cultures were performed for patients with fevers.

Questionnaires

We sent questionnaires (see Appendix in Supporting Information) to all participants after they gave consent to participate in the study. The questionnaires were designed to collect socio-demographic information, clinical history of gastroenteritis, and factors considered relevant for the disease, such as consumption of food items, water and beverages, dining location, travel history, contact with ill persons, animal contact, habits, medications taken, and previous morbidity.

Specimen collection and laboratory methods

A total of 335 stool samples were collected immediately in the ED, or within 3 days after discharge. For each participant, three specimens were collected, one native stool sample, one collected in Cary-Blair transport medium (BD Diagnostic Systems, Sparks, MD, USA), and one fixed and stained with Merthiolate-Iodine- Formaldehyde Fixative. All specimens were sent to the Centers for Disease Control, Taiwan, and were analysed for viruses (norovirus, rotavirus and astrovirus), parasites (*Giardia lamblia* and *Entamoeba histolytica*) and bacteria (suspected diarrhoeagenic *E. coli* (sDEC), *Salmonella* spp., *Shigella* spp., *Vibrio* spp., *Campylobacter* spp., *Aeromonas* spp. and *Staphylococcus aureus* with related enterotoxins). Parasites, sDEC and *Staphylococcus* with related enterotoxins were detected after March 2006. All specimens were cultured in blood agar plate (BAP), Xylose lysine deoxycholate agar (XLD) and selective agars (Salmonella Shigella agar (SS) for *Salmonella* spp. and *Shigella* spp., sorbitol MacConkey (SMAC) for Shiga toxin-producing *E. coli*, Thiosulfate Citrate Bile Salts Sucrose agar (TCBS) for *Vibrio* spp., and modified Charcoal Cefoperazone Deoxycholate agar (mCCDA) for *Campylobacter* spp.). The detection of the O serotyping for sDEC was performed as described previously [4]. Isolates that can agglutinate with one of the specific commercial pathogenic O antisera were defined as 'sDEC' isolates [5]. Rotaviruses and astroviruses were identified using enzyme-linked immunosorbent assays and RT-PCR; noroviruses were detected using RT-PCR only [6]. Amebiasis was detected using ProSpecT *Entamoeba histolytica* Microplate Assays (Remel Inc., Lenexa, Kansas, USA). Giardiasis was detected by semi-nested PCR [7].

A 10 mL blood specimen was also collected for each patient. All blood tests (including blood cultures) were performed at the Taipei City Hospital laboratory. The following tests were performed for all patients: C-reactive protein (CRP), white blood cell count (WBC) and biochemistry (blood urea nitrogen, creatine, aspartate transaminase, alanine transaminase, sodium, potassium and calcium).

Statistical analysis

Returned questionnaires were coded and data were entered into Epi Info (version 3.43) and analysed using SAS software (release 9.1). Any gastroenteritis was the outcome variable. We estimated univariate odds ratios (OR) and 95% confidence intervals (CI) using conditional logistic regression. The conditional logistic regression model with a stepwise selection procedure (p to enter <0.1; p to remove >0.05) was used to identify the most important determining factors for gastroenteritis. Finally, we estimated a population attributable risk fraction (PAR) for all risks in the final model using the method described by Bruzzi *et al.* [8].

Results

Descriptive epidemiology

Of the 1159 identified patients who met the study criteria, 419 (36.2%) returned completed and usable questionnaires. According to triage records, no differences were noted between participants and non-participants in terms of age, gender or distribution of diarrhoea symptoms, but non-participants exhibited more cases of vomiting and abdominal pain. Study participants with nausea, blood or mucus in their stools outnumbered their non-participant counterparts (Table 1). Study participants had higher maximum frequencies of daily diarrhoea compared with non-participants, but no difference was noted in frequencies of daily vomiting.

Of the 419 participants, 335 provided stool samples in the ED or within 3 days of discharge. At least one pathogen was detected in 201 (62.4%) of the samples. Viruses (40.0%) were identified as the leading cause of gastroenteritis, with noroviruses (33.2%) the most prevalent (Table 2). Bacteria were identified in 26.0% of the samples, with sDEC (22.2%) the most prevalent, followed by *Salmonella* spp. (5.4%) and *Vibrio parahaemolyticus* (4.2%). The only pathogenic parasite we identified was *Giardia lamblia* (16.4%). Distributions of microbiological findings between the first (1 August 2005 to 31 July 2006) and second study years were similar, although we did note an increase in norovirus frequency and a decrease in sDEC frequency during the second year. Of the 335 stool samples, 60 (17.9%) contained more than one

TABLE 1. Characteristics of participants and non-participants who met the study criteria

Characteristic	Participants (*n* = 419)	Non-participants (*n* = 740)	p*
Age (years)			
Median	35.0	34.0	0.605
Range	15–88	15–106	
Gender			
Male	185	333	0.781
Female	234	407	
Maximum frequency of diarrhoea in 1 day			
Median	6.0	5.0	<0.0001
Range	1–50	0–40	
Maximum frequency of vomiting in 1 day			
Median	3.0	3.0	0.911
Range	1–20	1–20	
Symptom distribution: number (%)			
Diarrhoea	365 (87.1)	660 (89.2)	0.294
Vomiting	186 (44.4)	419 (56.6)	<0.0001
Nausea	174 (41.5)	154 (20.8)	<0.0001
Abdominal pain	237 (56.6)	491 (66.4)	0.0009
Blood in stool	17 (4.1)	4 (0.5)	<0.0001
Mucus in stool	74 (17.7)	8 (1.1)	<0.0001

*Chi-square test used to calculate p values for gender and symptom distribution. Wilcoxon rank sum test used to calculate p value for age, maximum daily diarrhetic stool frequency, and maximum daily vomiting frequency.

pathogen. We also found that with a higher frequency of diarrhoea, starting from four times per day, there was a higher detection of positive pathogens (52.48% vs. 37.07%; p 0.005).

Symptoms reported by the 419 participants included diarrhoea (87.1%), abdominal pain (56.6%), general weakness (50.6%), vomiting (44.4%), nausea (41.5%), abdominal distension (29.6%), myalgia (29.4%), chill (29.1%), loss of appetite (28.2%), headache (20.5%), fever (20.3%), mucus in stool (17.7%), tenesmus (8.1%), blood in stool (4.1%), convulsions (2.1%) and skin rashes (2.1%). Maximum daily diarrhetic stool frequency median was 6.0 (range: 1–50; mode: 10.0). The median for maximum daily vomiting was 3.0 times (range, 1–20; mode, 1.0). Furthermore, 164 (39.1%) participants stated that they had taken prescription drugs for gastroenteritis before visiting the ED.

A total of 28 (6.7%) patients were admitted to the hospital. Antibiotics were given to cure 53 (12.6%) patients with severe gastroenteritis symptoms in the ED. Of the 87 patients with haemorrhoids, only six had blood in their stools; no statistically significant relationship was found between the two factors (p 0.13). Of the 86 patients exhibiting fever, two (2.3%) positive blood cultures of *Bacteroides fragilis* and *Aeromonas salmonicida* were found. Pus cells were found in 118 (35.2%) stool samples, and faecal occult blood was noted in 137 (40.9%); 77 (23.0%) samples had both. Mean CRP level was 15.1 (±20.1) mg/dL and mean WBC count 11.2 (±7.9) $\times 10^3/\mu$L. Respective percentages of neutrophils, lymphocytes, monocytes, eosinophils and basophils were 81.4 (±11.0), 12.6 (±8.6), 4.6 (±2.1), 1.2 (±1.1) and 0.3 (±0.2).

Of the 419 participants who returned usable questionnaires, 329 (78.1%) agreed to be interviewed by telephone

TABLE 2. Microbiological findings among participants, 1 August 2005 to 31 July 2007

	First study year *n* = 179		Second study year *n* = 156		Total *n* = 335[a]
	Number tested	Number (%) positive	Number tested	Number (%) positive	Number (%) positive
Viral pathogens	179	48 (26.8)	156	86 (55.1)	134 (40.0)
Norovirus	179	29 (16.2)	156	79 (50.6)	108 (33.2)
Rotavirus	179	16 (8.9)	156	7 (4.5)	23 (6.9)
Astrovirus	179	5 (2.8)	156	1 (0.6)	6 (1.8)
Bacterial pathogens	179	50 (27.9)	156	37 (23.7)	87 (26.0)
Shigella flexneri	179	0 (0.0)	156	1 (0.6)	1 (0.3)
Salmonella spp.	179	10 (5.6)	156	8 (5.1)	18 (5.4)
Vibrio parahaemolyticus	179	7 (3.9)	156	7 (4.5)	14 (4.2)
Aeromonas spp.	179	4 (2.2)	156	1 (0.6)	5 (1.5)
A. hydrophilla	179	3 (1.7)	156	0 (0.0)	3 (0.9)
A. salmonicida[b]	179	0 (0.0)	156	1 (0.6)	1 (0.3)
A. sobria	179	1 (0.6)	156	0 (0.0)	1 (0.3)
Suspected Diarrhoeagenic *E. coli*[b]	69	28 (40.6)	156	21 (13.5)	50 (22.2)
Campylobacter spp.	179	3 (1.7)	156	1 (0.6)	4 (1.2)
Plesiomonas shigelloides	179	1 (0.6)	156	1 (0.6)	2 (0.6)
Staphylococcus with related enterotoxin[b]	69	1 (1.4)	156	1 (0.6)	2 (0.9)
Bacteroides fragilis[c]	179	1 (0.5)	156	0 (0.0)	1 (0.3)
Pathogenic parasites[b]	69	8 (11.6)	156	29 (18.6)	37 (16.4)
Giardia lamblia[b]	69	8 (11.6)	156	29 (18.6)	37 (16.4)
Entamoeba histolytica[b]	69	0 (0.0)	156	0 (0.0)	0 (0.0)

[a]Of the 335 cases, one person was infected with a rotavirus and astrovirus; two were infected with a norovirus and rotavirus; one was infected with Giardia and a rotavirus; one with a norovirus and *Salmonella*; three with a norovirus, Giardia and diarrhoeagenic *E. coli* (DEC); two with Giardia and DEC; one with a norovirus, Giardia and *Staphylococcus*; two with a norovirus and *Salmonella*; 19 with a norovirus and DEC; 18 with a norovirus and Giardia; one with a norovirus, *Salmonella* and DEC; three with an astrovirus and DEC; one with *Salmonella*, Giardia and *Staphylococcus*; two with *Salmonella* and DEC; two with DEC and *Campylobacter*; and one with DEC and *Vibrio parahaemolyticus*.
[b]Suspected diarrhoeagenic *E. coli* (sDEC), *Staphylococcus* with related enterotoxins and pathogenic parasites were detected after March 2006.
[c]*Bacteroides fragilis* was isolated from blood samples. *Aeromonas salmonicida* was isolated from both blood and stool samples.

TABLE 3. Results from risk factor analysis for gastroenteritis in the study sample (338 paired participants)

	Univariate analysis		Multivariate model[a]		
Exposure	**OR**	**95% CI**	**Adjusted OR**	**95% CI**	**PAR (%)**
Being a student	1.80	1.10, 2.94	n.i.		
Taking antacids within 1 month prior to illness	3.17	1.99, 5.07	3.91	2.13, 7.15	17.6
Household members with gastroenteritis[b]	5.14	2.29, 11.55	5.18	2.09, 12.85	9.1
Attending a banquet[b]	2.50	1.75, 3.58	1.93	1.25, 2.98	19.6
Eating out[b]	3.70	2.26, 6.06	2.35	1.30, 4.23	50.9
Eating honey peaches[b]	2.56	1.18, 5.52	3.26	1.24, 8.58	5.6
Drinking bottled water[b]	1.96	1.38, 2.77	1.72	1.07, 2.75	19.7
Eating raw oysters[b]	3.70	1.38, 9.92	3.24	1.02, 10.28	3.2
Eating shrimp/crab[b]	2.23	1.53, 3.25	n.i.		
Attending open-air banquet[b]	5.00	1.10, 22.81	n.i.		
Eating at a Chinese/Western restaurant[b]	2.49	1.68, 3.68	n.i.		
Eating at a street caterer[b]	3.17	1.27, 7.93	n.i.		
Eating at a noodle shop[b]	1.76	1.21, 2.57	n.i.		
Eating cold side dish[b]	1.91	1.23, 2.98	n.i.		
Eating salad[b]	1.54	1.03, 2.29	n.i.		
Eating raw fish[b]	1.73	1.09, 2.77	n.i.		
Eating clam/shells[b]	1.68	1.15, 2.46	n.i.		
Eating pork[b]	2.11	1.30, 3.45	n.i.		
Eating beef[b]	1.15	0.81, 1.62	n.i.		
Changing a diaper[b]	1.93	1.04, 3.61	n.i.		

OR, odds ratio; CI, confidence interval; PAR, population attributable risk fraction; n.i., not in final model.
[a]Odds ratio and 95% confidence interval derived from conditional logistic regression with a stepwise selection procedure.
[b]Exposed to this factor within 1 week prior to illness.

within 2 weeks of discharge. The appearance of new symptoms after leaving the ED was reported by 50 (15.2%) patients, with symptom distributions similar to those reported in the questionnaires. Median illness duration was 1.0 day (range, 1–22; mode, 2.0). A total of 43 (10.3%) patients reported that family members, co-workers or friends had experienced the same symptoms 7 days or less prior to their ED visits.

Matched case-control study

Of 482 enrolled patients with non-gastroenteritis who met the study criteria, 338 (70.1%) returned completed questionnaires. Our case-control study sample consisted of 338 matched pairs (142 male, 196 female). Average time intervals from patients' first presentation at the ED to recruitment of their controls were 5.4 days for men and 5.6 days for women. Results of univariate analysis showing factors significantly associated with gastroenteritis are presented in Table 3. Statistical significance was not found for education level, size of house, travel, contact with sick children, touching pets or other animals, swimming, not washing hands before a meal, washing hands without soap, shaking hands with another person, frequent or recent hugging or kissing, taking H_2 antagonists or proton pump inhibitors, having taken steroids before illness, having taken Chinese medicine, hypertension, diabetes or asthma.

According to our results from the final multivariate conditional logistic (stepwise) analysis (Table 3), only seven variables were found to have statistically significant associations with the gastroenteritis cases: attending a banquet (means a ceremonious feast) (adjusted OR = 1.93; 95% CI, 1.25, 2.98), eating out (adjusted OR = 2.35; 95% CI, 1.30, 4.23), taking antacids before the illness (adjusted OR = 3.91; 95% CI, 2.13, 7.15), household members with gastroenteritis (adjusted OR = 5.18, 95% CI: 2.09, 12.85), drinking bottled water (adjusted OR = 1.72; 95% CI, 1.07, 2.75), eating honey peaches (adjusted OR = 3.26; 95% CI, 1.24, 8.58), and eating raw oysters (adjusted OR = 3.24; 95% CI, 1.02, 10.28). Eating out had the highest impact as measured by PAR (Table 3). PAR for all significant risk factors together was 78.3%.

Discussion

This is the first ED-based study on the risk factors of gastroenteritis in adolescents and adults in Taiwan. This study shows that viruses were the leading cause of gastroenteritis, and the associations between presentation to the ED for gastroenteritis and eating out, attending a banquet, infectious household members, taking antacids, eating honey peaches, eating raw oysters and drinking bottled water.

Recall bias is still an issue in our study, even though we provided the respondents with a list of possible exposures to reduce errors due to memory omission; however, cases might show greater motivation to respond to questionnaires than controls. Selection bias may exist because of a low response rate of ED cases and greater diarrhoea frequency in enrolled cases. In our study, more severe cases were found. According to Tam *et al.* [9], we can suspect that more

severe cases would identify some specific factors (i.e. eating out) associated with severe but not mild disease.

Because the examinations of sDEC, *Staphylococcus* with related enterotoxins and parasites were not conducted until March 2006, the positive rates for these pathogens didn't reflect the first-year information as compared with other pathogens detected. *Clostridium difficile* was not thought to be a dominant pathogen for community-acquired diarrhoea until Huhulescu *et al.* proved that it was [10]. Therefore, the isolation of *Clostridium difficile* was not considered necessary in our study. In addition, our finding tends to overestimate the positive detection rate of DEC by using the O serotyping method alone according to Yang *et al.* [4].

Some of our patients were diagnosed with co-infection with norovirus and other pathogens. Amar *et al.* [11] detected norovirus in cases and asymptomatic controls by RT-PCR. On the other hand, Phillips *et al.* [12] used the method of viral load with real time RT-PCR to identify that healthy people can be positive and cases may shed low levels of norovirus, indicating that the virus may not be the cause of their illness. Therefore, a substantial number of cases at the ED level may have coincidental norovirus infection with disease actually caused by another pathogen because of the over-representation of pathogens causing more severe disease compared with the distribution of pathogens in the community.

Our finding of viruses as the leading cause of gastroenteritis cases and the predominance of noroviruses in both adolescents and adults agrees with previous reports [10,11,13,14]. A strong association and high PAR values were found between eating out and gastroenteritis risk. This finding agrees with those from a UK study showing a strong connection between eating out and food poisoning cases at an ED (OR = 2.41; 95% CI, 1.29, 4.50) [3], but a lower rate of positive pathogens was found (16.9%) and no virus was detected in the study. The finding of higher PAR for eating out may reflect the fact that pathogens contracted through food-borne transmission cause more severe illness than those that are transmitted person-to-person.

Another German study indicated that *Campylobacter* spp. (35%) was identified as the leading cause of hospitalized adults with acute gastroenteritis, followed by norovirus (23%), *Salmonella* spp. (20%) and rotavirus (15%) [15]. The different spectrum of pathogens between the Germany study and ours was attributed to different detection methods and different study population groups. The high proportion of *Campylobacter spp.* infections found is most likely explained by additional use of serological testing in their study. Hospitalized patients have more severe illness than ED patients; therefore, this could result in a different spectrum of pathogens. In addition, the rate of mixed infections (22%) in their study was higher than ours (17.9%). Therefore, mixed infections should be one of the causes of severe gastroenteritis. One study showed that pathogens are more frequently isolated in a severe episode [16]. We also observed a higher positive pathogen detection rate for patients with a daily frequency of four or more episodes of diarrhoea.

Note that while attending a banquet has been associated with outbreaks of gastroenteritis [17], ours is the first study to report an elevated risk for sporadic gastroenteritis. A strong association was found between instances of gastroenteritis and taking antacids in the month previously (17.6% PAR). Because gastric acid is capable of killing ingested bacteria [18], decreased gastric acidity is a risk factor for infectious diarrhoea-related illnesses, such as travelers' diarrhoea, salmonellosis, cholera, campylobacteriosis and diseases associated with *C. perfringens* and *C. difficile* [19]. Our data also indicate no association between proton pump inhibitors or H_2 antagonists and gastroenteritis. However, these patients constituted a small percentage of our sample. A larger sample size is thus needed to better power the study to look at this association.

Regarding the strong association between other household members having gastroenteritis and our participants suffering from gastroenteritis, household transmission is a known risk factor for rotaviruses, noroviruses, *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., DEC, *Giardia*, *Cryptosporidium* spp. [20,21] and *Vibrio cholerae* [22]. The association between honey peach consumption and gastroenteritis could be expected because the peach was not properly washed before consumption, and/or it was not peeled before eating.

There are many studies showing that eating raw oysters significantly increases the risk of gastroenteritis, as indicated in our final model. Research teams have reported associations with rotaviruses, astroviruses, Aichi viruses, noroviruses [23], *Vibrio* spp. [24], *Shigella sonnei* [25], and non-O group 1 *Vibrio cholerae* [26]. Researchers have isolated *Vibrio vulnificus* [27] and *Aeromonas hydrophila* [28] from locally harvested oysters in Taiwan. We could not confirm any connection between laboratory findings of pathogens in stool samples and the presence of pathogens in oysters, because no oyster pathogen monitoring took place in Taiwan during the study period.

We were surprised by the finding of a statistical association between bottled water consumption and gastroenteritis in Taipei. A UK study showed that persons with *Campylobacter coli* infection were more likely to have drunk bottled water than were those with *Campylobacter jejuni* infection [29]. Another study showed that norovirus was detected in two brands of mineral water [30], but the potential connec-

tion between bottled water and norovirus gastroenteritis risk has never been documented.

In summary, our results are consistent with those from previous studies on gastroenteritis with one important exception: bottled water. More detailed studies are required regarding the detection of *Clostridium difficile* and DEC, and pathogen distribution in a healthy population. Studies on bottled water-associated gastroenteritis and pathogen-specific risks are also needed.

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Transparency Declaration

Financial support was provided by the Taiwan Centers for Disease Control and the Taipei City Health Department. All the authors declare that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Questionnaire of Gastroenteritis Investigation.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

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